IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, v. DEY, L.P., and DEY, INC. Defendants.	C.A. No. 06-113 (JJF) C.A. No. 06-604 (JJF) CONSOLIDATED **REDACTED – PUBLIC VERSION**
SEPRACOR INC., Plaintiff, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 07-438 (JJF)

DECLARATION OF PRESTON K. RATLIFF II IN SUPPORT OF SEPRACOR'S OPENING CLAIM CONSTRUCTION BRIEF

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Original Filing Date: April 10, 2008
Redacted Filing Date: April 16, 2008

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SEPRACOR INC., Plaintiff, v. DEY, L.P., and DEY, INC. Defendants.	C.A. No. 06-113 (JJF) C.A. No. 06-604 (JJF) CONSOLIDATED
SEPRACOR INC., Plaintiff, v. BARR LABORATORIES, INC., Defendant.	C.A. No. 07-438 (JJF) **REDACTED – PUBLIC VERSION**

DECLARATION OF PRESTON K. RATLIFF II IN SUPPORT OF SEPRACOR'S OPENING CLAIM CONSTRUCTION BRIEF

I, Preston K. Ratliff II, am associated with the law firm of Paul, Hastings, Janofsky & Walker LLP, counsel for Plaintiff, Sepracor Inc. ("Sepracor"). I make this declaration in support of SEPRACOR'S OPENING CLAIM CONSTRUCTION BRIEF.

1. Attached as Exhibit 1 hereto is a true and correct copy of U.S. Patent No. 5,362,755.

2. Attached as Exhibit 2 hereto is a true and correct copy of U.S. Patent No. 5,547,994.

3. Attached as Exhibit 3 hereto is a true and correct copy of U.S. Patent No. 5,760,090.

4. Attached as Exhibit 4 hereto is a true and correct copy of U.S. Patent No. 5,844,002.

5. Attached as Exhibit 5 hereto is a true and correct copy of U.S. Patent 6,083,993.

6. Attached as Exhibit 6 hereto is a true and correct copy of a May 12, 1994 Submission to the USPTO regarding application no. 08/163,581.

7. Attached as Exhibit 7 hereto is a true and correct copy of a July 26, 1994 communication from the USPTO regarding application no. 08/163,581.

8. Attached as Exhibit 8 hereto is a true and correct copy of a July 14, 1992 Submission to the USPTO regarding application no. 07/896,725.

9. Attached as Exhibit 9 hereto is a true and correct copy of a March 26, 2008 letter from Imron T. Aly to Preston K. Ratliff II.

10. Attached as Exhibit 10 hereto is a true and correct copy of a May 11, 1994 declaration of T. Scott Johnson submitted to the USPTO in application no. 08/163,581.

11. Attached as Exhibit 11 hereto is a true and correct copy of a June 9, 1995 Submission to the USPTO regarding application no. 08/335,480.

12. Attached as Exhibit 12 hereto is a true and correct copy of Stedman's Medical Dictionary, 25th Edition, page 214.

13. Attached as Exhibit 13 hereto is a true and correct copy of the Second Supplemental Response of Defendants Dey, L.P. and Dey, Inc. to Plaintiff's Interrogatories Nos. 1, 2, 4, 5, 7, and 8.

14. Attached as Exhibit 14 hereto is a true and correct copy of an April 21, 1998 Submission to the USPTO regarding application no. 09/063,551.

15. Attached as Exhibit 15 hereto is a true and correct copy of A. Lurie et al., *Long Term Management of Reversible Obstructive Airways Disease in Adults*, Lung (1990) Suppl:154-167.

16. Attached as Exhibit 16 hereto is a true and correct copy of a December 17, 1999 Submission to the USPTO regarding application no. 09/200,541.

I declare under penalty of perjury that the foregoing is true and correct.

Dated: 4/10/08

Preston K. Ratliff II

CERTIFICATE OF SERVICE

I, hereby certify that on April 16, 2008, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

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I also certify that copies were caused to be served on April 16, 2008 upon the following in the manner indicated:

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EXHIBIT 1

US005362755A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,362,755

[45] Date of Patent: Nov. 8, 1994

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Yonng, Still River, both of Mass.

[73] Assignee: Sepracor, Inc., Marlborough, Mass.

[21] Appl. No.: 163,581

[22] Filed: Dec. 7, 1993

Related U.S. Application Data

[63] Continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[5] A61K 31/135

[52] U.S. Cl. 514/649; 514/826

[58] Field of Search 514/649, 826

[56] References Cited

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2255503 7/1992 United Kingdom .

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Primary Examiner—Raymond J. Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg

[57] ABSTRACT

The optically pure R(−) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(−) isomer of albuterol for treating asthma while minimizing the side effects associated with chronic administration of racemic albuterol.

7 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

This application is a continuation of application Ser. No. 07/896,725 filed Jun. 9, 1992 now abandoned which is a continuation of copending application Ser. No. 07/461,262 filed on Jan. 5, 1990 now abandoned.

DESCRIPTION

1. Background

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent broncho-dilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(-tert-butylamino) methyl]-4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the

optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(−) isomer of albuterol is greater than approximately 90% by weight of total albuterol.

3. A method of claim 2 wherein the amount of the R(−) isomer of albuterol is greater than 99% by weight of total albuterol.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(−) isomer of albuterol per dose.

5. A method of claim 1 comprising orally administering to the individual from approximately 1 mg to approximately 8 mg of the R(−) isomer of albuterol two to four times daily.

6. A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration or racemic albuterol, comprising chronically administering to the individual a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

7. A method of claim 6 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

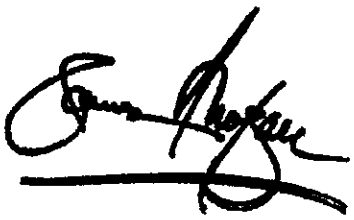
PATENT NO. : 5,362,755
DATED : November 8, 1994
INVENTOR(S) : Barbarich et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 4,
Line 30, delete the word "or" and insert the word -- of --

Signed and Sealed this

Thirtieth Day of September, 2003



JAMES E. ROGAN
Director of the United States Patent and Trademark Office

EXHIBIT 2

US005547994A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,547,994

[45] Date of Patent: Aug. 20, 1996

[54] **METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[21] Appl. No.: **335,480**

[22] Filed: **Nov. 7, 1994**

Related U.S. Application Data

[63] Continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649, 826

[56] **References Cited**

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5,362,755 11/1994 Barberich et al. 514/649

FOREIGN PATENT DOCUMENTS

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

6 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 and now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992, now abandoned, which was a continuation of application Ser. No. 07/461,262 filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(–) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(–) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(–) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(–) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(–) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1 [(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(–) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(–) isomer of albuterol is administered to an individual who has asthma. For example, R(–) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(–) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(–) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(–) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(–) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(–) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(–) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a par-

ticular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(–) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(–) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method of claim 1 wherein the amount of the R(–) isomer of albuterol is greater than approximately 90% by weight.

3. A method of claim 2 wherein the amount of the R(–) isomer of albuterol is greater than 99% by weight.

4. A method of claim 1 comprising administering to the individual by inhalation from approximately 30 mcg to approximately 90 mcg of the R(–) isomer of albuterol per dose.

5. A method of treating an acute attack of asthma, while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to an individual suffering from an acute attack of asthma a quantity of an optically pure R(–) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

6. A method of claim 5 wherein the analgesic is selected from the group consisting of: aspirin, acetaminophen and ibuprofen.

* * * * *

EXHIBIT 3

US005760090A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,760,090

[45] Date of Patent: *Jun. 2, 1998

[54] METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[*] Notice: The term of this patent shall not extend beyond the expiration date of Pat. No. 5,362,755.

[21] Appl. No.: **691,604**

[22] Filed: **Aug. 15, 1996**

Related U.S. Application Data

[63] Continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649

[56] **References Cited**

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Morley et al. "Effects of (+) and racemic salbutamol on airway responses in the guinea pig" *Brit. J. Pharmacol.* 104, 295P (1991).

Chapman et al. "Racemic mixtures at root of worsening symptom? Active enantiomers . . . " *TIPS* 13, 231–232 (1992).

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Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

9 Claims, No Drawings

METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(−) ALBUTEROL

This is a continuation of U.S. application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of U.S. application Ser. No. 08/163,581 filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which is a continuation of U.S. application Ser. No. 07/896,725, filed Jun. 9, 1992, abandoned, which is a continuation of U.S. application Ser. No. 07/461,262, filed Jan. 5, 1990, abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from

bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or

propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of treating asthma, while reducing side effects associated with the administration of racemic albuterol, comprising administering to an individual suffering from asthma a quantity of an optically pure R(−) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

2. A method according to claim 1, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim 1, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim 1, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim 4, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim 1, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim 6, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim 6, wherein the optically pure R(−) albuterol is administered as a syrup.

9. A method according to claim 7, wherein the optically pure R(−) albuterol is administered as a syrup.

* * * * *

EXHIBIT 4

US005844002A

United States Patent [19]

Barberich et al.

[11] Patent Number: 5,844,002

[45] Date of Patent: Dec. 1, 1998

[54] **METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(–) ALBUTEROL**

[75] Inventors: **Timothy J. Barberich**, Concord; **James W. Young**, Still River, both of Mass.

[73] Assignee: **Sepracor, Inc.**, Marlborough, Mass.

[21] Appl. No.: **63,551**

[22] Filed: **Apr. 21, 1998**

Related U.S. Application Data

[63] Continuation of Ser. No. 691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of Ser. No. 335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of Ser. No. 163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of Ser. No. 896,725, Jun. 9, 1992, abandoned, which is a continuation of Ser. No. 461,262, Jan. 5, 1990, abandoned.

[51] **Int. Cl.**[6] **A61K 31/135**

[52] **U.S. Cl.** **514/649**; 514/826

[58] **Field of Search** 514/649, 826

[56] **References Cited**

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Passowicz–Muszynska E. "Effect on beta adrenergic receptors of tachyphylaxis . . . " *Index Medicus* 91:164287.

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr.* 89: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] **ABSTRACT**

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

10 Claims, No Drawings

METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which is a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which is a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993 now U.S. Pat. No. 5,362,755, which is a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on beta$_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may have an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs. In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the broncho-dilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl] -4-hydroxy-m-xylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more)

drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(–) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(–) isomer may reduce the teratogenic potential associated with albuterol.

Equivalents

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

We claim:

1. A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(–) albuterol sufficient to induce said bronchodilation.

2. A method according to claim **1**, wherein the albuterol comprises at least 90% by weight of the R(–) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim **1**, wherein the albuterol comprises at least 99% by weight of the R(–) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim **1**, wherein the optically pure R(–) albuterol is administered by inhalation.

5. A method according to claim **4**, wherein the optically pure R(–) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim **1**, wherein the optically pure R(–) albuterol is administered orally.

7. A method according to claim **6**, wherein the optically pure R(–) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim **6**, wherein the optically pure R(–) albuterol is administered as a syrup.

9. A method according to claim **7**, wherein the optically pure R(–) albuterol is administered as a syrup.

10. A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically pure R-(–) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

* * * * *

EXHIBIT 5

US006083993A

United States Patent [19]

Barberich et al.

[11] Patent Number: 6,083,993

[45] Date of Patent: *Jul. 4, 2000

[54] METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(–) ALBUTEROL

[75] Inventors: Timothy J. Barberich, Concord; James W. Young, Still River, both of Mass.

[73] Assignee: Sepracor Inc., Marlborough, Mass.

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: 09/466,107

[22] Filed: Dec. 17, 1999

Related U.S. Application Data

[63] Continuation of application No. 09/200,541, Nov. 25, 1998, which is a continuation of application No. 09/063,551, Apr. 21, 1998, Pat. No. 5,844,002, which is a continuation of application No. 08/691,604, Aug. 15, 1996, Pat. No. 5,760,090, which is a continuation of application No. 08/335,480, Nov. 7, 1994, Pat. No. 5,547,994, which is a continuation of application No. 08/163,581, Dec. 7, 1993, Pat. No. 5,362,755, which is a continuation of application No. 07/896,725, Jun. 9, 1992, abandoned, which is a continuation of application No. 07/461,262, Jan. 5, 1990, abandoned.

[51] Int. Cl.[7] A61K 31/135

[52] U.S. Cl. 514/649

[58] Field of Search 514/649

[56] References Cited

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Muittari et al. "Comparison of acute bronchodilator effects of oral salbutamol, . . . " *Chem. Abstr. 89*: 123259m (1978).

Primary Examiner—Raymond Henley, III

Attorney, Agent, or Firm—Heslin & Rothenberg, P.C.

[57] ABSTRACT

The optically pure R(–) isomer of albuterol, which is substantially free of the S(+) isomer, is a potent bronchodilator for relieving the symptoms associated with asthma in individuals. A method is disclosed utilizing the optically pure R(–) isomer of albuterol for treating asthma while minimizing the side effects associated with albuterol.

17 Claims, No Drawings

METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(−) ALBUTEROL

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation of our prior copending application Ser. No. 09/200,541, filed Nov. 25, 1998, which is a continuation of application Ser. No. 09/063,551, filed Apr. 21, 1998, now U.S. Pat. No. 5,844,002, which was a continuation of application Ser. No. 08/691,604, filed Aug. 15, 1996, now U.S. Pat. No. 5,760,090, which was a continuation of application Ser. No. 08/335,480, filed Nov. 7, 1994, now U.S. Pat. No. 5,547,994, which was a continuation of application Ser. No. 08/163,581, filed Dec. 7, 1993, now U.S. Pat. No. 5,362,755, which was a continuation of application Ser. No. 07/896,725, filed Jun. 9, 1992 now abandoned, which was a continuation of application Ser. No. 07/461,262, filed Jan. 5, 1990, now abandoned.

BACKGROUND

Albuterol is a drug belonging to the general class of beta-adrenergic compounds. The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (AMP) from adenosine triphosphate (ATP). The cyclic AMP formed mediates the cellular responses. Albuterol acts selectively on $beta_2$-adrenergic receptors to relax smooth muscle tissue, for example, in the bronchial system. Albuterol is most commonly used to treat bronchial spasms associated with asthma and is the active component in well-known commercial bronchodilators such as Proventil and Ventolin.

The form in which albuterol is presently used is a racemic mixture. That is, it is a mixture of optical isomers, called enantiomers. Enantiomers are structurally identical compounds which differ only in that one isomer is a mirror image of the other and the mirror images cannot be superimposed. This phenomenon is known as chirality. Most biological molecules exist as enantiomers and exhibit chirality. Although structurally identical, enantiomers can have profoundly different effects in biological systems: one enantiomer may have a specific biological activity while the other enantiomer has no biological activity at all, or may nave an entirely different form of biological activity.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating bronchial disorders, such as asthma, in an individual, by administering to the individual an amount of optically pure R(−) albuterol which is active in bronchial tissue sufficient to reduce bronchial spasms associated with asthma while minimizing side effects associated with albuterol. The method is particularly useful in treating asthma while reducing side effects, such as central nervous system stimulatory effects and cardiac arrythmia. In these applications, it is important to have a composition which is a potent bronchodilator and which does not exhibit the adverse side effects of many beta-adrenergic drugs. A composition containing the pure R(−) isomer of albuterol is particularly useful for this application because this isomer exhibits these desired characteristics. The present method provides a safe, effective method for treating asthma while reducing undesirable side effects, for example, tremor, nervousness, shakiness, dizziness and increased appetite, and particularly, cardiac arrythmia, typically associated with beta-adrenergic drugs.

In children, side effects such as excitement, nervousness and hyperkinesia are reduced when the pure isomer is administered. In addition to the above, at certain levels racemic albuterol can cause teratogenic effects, which are believed to be associated with the S(+) isomer. Administering the pure isomer reduces the teratogenic potential which is associated with the S(+) isomer of albuterol.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relies on the bronchodilation activity of the R(−) enantiomer of albuterol to provide relief from bronchial disorders, while simultaneously reducing undesirable side effects, for example, central nervous system stimulatory effects and cardiac disorders, commonly experienced by albuterol users. In the present method, the optically pure R(−) isomer of albuterol, which is substantially free of the S(+) enantiomer, is administered alone, or in combination with one or more other drug(s) in adjunctive treatment, to an individual in whom asthma relief (e.g., relief from bronchial spasms, shortness of breath) is desired. The optically pure R(−) isomer of albuterol as used herein refers to the levorotatory optically pure isomer of α^1[(tert-butylamino) methyl]-4-hydroxy-mxylene-α, α'-diol, and to any biologically acceptable salt or ester thereof. The terms "optically pure" or "substantially free of the S(+) enantiomer" as used herein means that the composition contains at least 90% by weight of the R(−) isomer of albuterol and 10% by weight or less of the S(+) isomer. Optically pure albuterol is readily obtainable by methods known to those of skill in the art, for example, by synthesis from an optically pure intermediate.

In the present method, the R(−) isomer of albuterol is administered to an individual who has asthma. For example, R(−) albuterol is administered to an individual after onset of asthma to reduce breathing difficulty resulting from asthma. In another embodiment, optically pure R(−) albuterol is administered prophylactically, that is, before the bronchiospasm begins in an asthma attack, to prevent its occurrence or to reduce the extent to which it occurs.

In the present method, R(−) albuterol can be administered by inhalation, by subcutaneous or other injection, orally, intravenously, topically, parenterally, transdermally, rectally or via an implanted reservoir containing the drug. The form in which the drug will be administered (e.g., inhalant, powder, tablet, capsule, solution, emulsion) will depend on the route by which it is administered. The quantity of the drug to be administered will be determined on an individual basis, and will be based at least in part on consideration of the individual's size, the severity of the symptoms to be treated and the result sought. In general, quantities of optically pure R(−) albuterol sufficient to reduce the symptoms of asthma will be administered. The actual dosage (quantity administered at a time) and the number of administrations per day will depend on the mode of administration, for example, by inhaler, nebulizer or oral administration. About 30 mcg to about 90 mcg of the optically pure R(−) isomer of albuterol given by inhalation one or more times per day will be adequate in most individuals to produce the desired bronchodilation effect. For oral administration, e.g., tablet or syrup, a dose of about 1 mg to about 8 mg two to four times daily is administered to produce the desired effect.

In the method of the present invention, the optically pure R(−) isomer of albuterol can be administered together with one or more other drug(s). For example, an antiasthmatic drug such as theophylline or terbutaline, or an antihistamine

or analgesic such as aspirin, acetaminophen or ibuprofen, can be given with or in close temporal proximity to administration of optically pure, R(−) albuterol. The two (or more) drugs (the optically pure active isomer of albuterol and another drug) can be administered in one composition or as two separate entities. For example, they can be administered in a single capsule, tablet, powder, or liquid, etc. or as individual compounds. The components included in a particular composition, in addition to optically pure albuterol and another drug or drugs, are determined primarily by the manner in which the composition is to be administered. For example, a composition to be administered in inhalent form can include, in addition to the drug(s), a liquid carrier and/or propellent. A composition to be administered in tablet form can include a filler (e.g., lactose), a binder (e.g., carboxymethyl cellulose, gum arabic, gelatin), an adjuvant, a flavoring agent, a coloring agent and a coating material (e.g., wax or a plasticizer). A composition to be administered in liquid form can include the combination of drugs and, optionally, an emulsifying agent, a flavoring agent and/or a coloring agent.

In general, according to the method of the present invention, the optically pure R(−) isomer of albuterol, alone or in combination with another drug(s), is administered to an individual periodically as necessary to reduce symptoms of asthma.

The present composition and method provide an effective treatment for asthma while minimizing the undesirable side effects associated with albuterol use. These side effects include central nervous system effects, such as tremor, nervousness, shakiness, dizziness and increased appetite, and cardiac effects, such as cardiac arrythmia. In children, side effects, such as excitement, nervousness and hyperkinesia, are reduced when the pure isomer is administered. In addition, teratogenic effects associated with albuterol are believed to reside in the S(+) enantiomer. Thus, administering the pure R(−) isomer may reduce the teratogenic potential associated with albuterol.

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed in the scope of the following claims.

What is claimed is:

1. A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

2. A method according to claim **1**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

3. A method according to claim **1**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

4. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered by inhalation.

5. A method according to claim **4**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

6. A method according to claim **1**, wherein the optically pure R(−) albuterol is administered orally.

7. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

8. A method according to claim **6**, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

9. A method according to claim **7**, wherein the optically pure R(−) albuterol is administered as a syrup.

10. A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(−) albuterol.

11. A method according to claim **10**, wherein the albuterol comprises at least 90% by weight of the R(−) isomer and not more than 10% by weight of the S(+) isomer.

12. A method according to claim **10**, wherein the albuterol comprises at least 99% by weight of the R(−) isomer and 1% or less by weight of the S(+) isomer.

13. A method according to claim **10**, wherein the optically pure R(−) albuterol is administered by inhalation.

14. A method according to claim **13**, wherein the optically pure R(−) albuterol is administered in an amount of about 30 μg to about 90 μg.

15. A method according to claim **10**, wherein the optically pure R(−) albuterol is administered orally.

16. A method according to claim **15**, wherein the optically pure R(−) albuterol is administered in an amount of about 1 mg to about 8 mg.

17. A method according to claim **15**, wherein the optically pure R(−) albuterol is administered as a tablet, capsule or syrup.

* * * * *

EXHIBIT 6

SPC8905

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/163,581 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: R. Henley

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R)-ALBUTEROL

CERTIFICATE OF TRANSMISSION

I hereby certify that this correspondence is being facsimile transmitted to the Patent and Trademark Office:

on May 12, 1994

Philip E Hansen

Signature

Philip E. Hansen

Typed or printed name of person signing certificate

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

This is in response to the office action of February 25, 1994, to which response is required by May 25, 1994; this response is therefore timely filed. The response, in the first part, addresses the issues raised in the office action of February 25 and, in the second part, responds to issues raised in the interview graciously granted by Examiner Henley with applicants' undersigned agent on May 3, 1994.

AMENDMENT

Please cancel claims 15 to 18.

Please amend claim 1 as follows:

1. (Amended) A method of treating asthma in an individual with albuterol, while reducing side effects associated with chronic administration of racemic albuterol, comprising chronically administering to the individual a quantity of an

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optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

REMARKS

Claims 1-6, 8 and 15-18 were present in the application as filed under 37 CFR 1.62. Claims 15 to 18 are canceled by amendment above. Claims 1-6 and 8 are therefore pending in the application.

In the office action of February 25, claims 1-6 were rejected under 35 USC §103 as obvious over Muittari et al. (Chem. Abs. 89:12359m). As explained in the Preliminary Remarks submitted December 7, 1993, Muittari deals strictly with the effects of racemic albuterol. Applicants do not believe Muittari could suggest anything about the advantages attendant upon the use of a single enantiomer.

Claims 1-6 and 8 were also rejected over Brittain et al., Hartley et al. and Buckner et al. As explained in the interview of May 3, and in the Preliminary Remarks of December 7, each of the Brittain, Hartley and Buckner references discusses the pharmacology of the individual enantiomers, but none suggests any advantage in diminution of side effects to be gained from the use of the pure R enantiomer, which is the substance of applicants' claimed invention.

Applicants have found that when isolated guinea pig tracheal muscle preparations were subjected to graded doses of a spasmogen, the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. They concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on

bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. and Chapman et al. (references provided with the response of February 16, 1993) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. British patent application 2,255,503, filed (by Morley and Chapman) more than a year after applicants' '262 application, makes a similar disclosure and presents claims very similar to applicants'.

After reviewing the foregoing issues in the interview of May 3, the examiner indicated that he felt there might be patentable subject matter related to avoidance of side effects that show up on chronic medication with racemic albuterol. He felt that a claim in the format of amended claim 1 above could be allowable if two issues could be resolved: (1) whether support exists in the specification for the restriction of the method to avoidance of side effects in chronic therapy and (2) whether Dr. Aberg's showing of July 23, 1993, is commensurate with the original disclosure.

The first of these concerns is addressed in the accompanying declaration under 37 CFR 1.132 of T. Scott Johnson, M.D. Dr. Johnson explains that although the term "chronic" does not appear in the specification as originally filed, the person of ordinary skill in the art would expect that albuterol would be given chronically, since that is the common mode of therapy. Moreover, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, and page 5, line 6 to line 9, the prophylactic therapy described makes medical sense only if chronic administration is intended.

As to the second point, applicants' agent believes that

the seminal case on the question of the correspondence between a showing and the scope of the original disclosure that he and the examiner were seeking is *In re Zenitz* (142 USPQ 158). Zenitz was claiming compounds and applicants are claiming a method of use, so the analogy is not perfect, but the reasoning appears apposite. In *Zenitz* the applicant had disclosed that the compounds sought to be patented were useful as sedatives and hypotensive agents, but had not discussed any separation between sedation and hypotensive effects as an advantage of his compounds. In support of the unobviousness of the compounds, he provided an affidavit showing the unexpected separation of hypotensive and sedative effects in certain of these compounds. The examiner held, and the Board of Appeals affirmed, that since the separation of effects was not originally disclosed, Zenitz could not rely on that in his showing.

However, the CCPA reversed the decision of the Board of Appeals on the basis that the unexpected utility, although not specifically disclosed, would nevertheless flow from the disclosed utility. Applicants believe that the same reasoning applies to their situation: applicants did not specifically disclose airway hyperreactivity as a side effect to be avoided by the use of the pure R isomer; however, airway hyperreactivity is certainly a side effect and avoiding airway hyperreactivity could be said to reasonably flow from the disclosure of avoiding side effects. Thus applicants believe that the declaration of Dr. Gunnar Aberg submitted July 23, 1993, and the articles by Chapman and Morley reinforcing that declaration, provide appropriate support for the claims to "avoiding side effects" consistent with the holding of the CCPA in *Zenitz*.

The CCPA in *Zenitz* distinguished their decision from *In re Herr* (134 USPQ 176). In *Herr*, the utility disclosed for

the compounds sought to be patented was solely as chemical intermediates and the affidavit proffered by Herr alleged utility as anabolic and androgenic agents. The court found that the anabolic and androgenic utility would not flow from their disclosed utility as intermediates. Applicants believe that the situation in the present case is analogous to *Senitz* and can be distinguished from *Herr* on the same basis as that provided by the CCPA.

In light of the foregoing amendment, declaration and explanation, it is believed that the application is in condition for allowance and such is respectfully requested.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: May 12, 1994

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EXHIBIT 7

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/163,581	12/07/93	BARBERICH	I SPC8905

EXAMINER
HENLEY III,R

12M1/0726

ART UNIT	PAPER NUMBER
1205	10

PHILIP E. HANSEN
HESLIN & ROTHENBERG, P.C.
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ALBANY, NY 12203-5160

DATE MAILED: 07/26/94

7-22-94

NOTICE OF ALLOWABILITY

PART I.

1. ☒ This communication is responsive to the amendment + declaration filed May 11, 1994
2. ☒ All the claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice Of Allowance And Issue Fee Due or other appropriate communication will be sent in due course.
3. ☒ The allowed claims are 1-6 and 8 (renumbered as 1-7 respectively).
4. ☐ The drawings filed on _____ are acceptable.
5. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has [_] been received. [_] not been received. [_] been filed in parent application Serial No. _____, filed on _____.
6. ☒ Note the attached Examiner's Amendment.
7. ☒ Note the attached Examiner Interview Summary Record, PTOL-413.
8. ☒ Note the attached Examiner's Statement of Reasons for Allowance.
9. ☐ Note the attached NOTICE OF REFERENCES CITED, PTO-892.
10. ☐ Note the attached INFORMATION DISCLOSURE CITATION, PTO-1449.

PART II.

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" indicated on this form. Failure to timely comply will result in the ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

1. ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
2. ☐ APPLICANT MUST MAKE THE DRAWING CHANGES INDICATED BELOW IN THE MANNER SET FORTH ON THE REVERSE SIDE OF THIS PAPER.
   a. ☐ Drawing informalities are indicated on the NOTICE RE PATENT DRAWINGS, PTO-948, attached hereto or to Paper No. _____. CORRECTION IS REQUIRED.
   b. ☐ The proposed drawing correction filed on _____ has been approved by the examiner. CORRECTION IS REQUIRED.
   c. ☐ Approved drawing corrections are described by the examiner in the attached EXAMINER'S AMENDMENT. CORRECTION IS REQUIRED.
   d. ☐ Formal drawings are now REQUIRED.

Any response to this letter should include in the upper right hand corner, the following information from the NOTICE OF ALLOWANCE AND ISSUE FEE DUE: ISSUE BATCH NUMBER, DATE OF THE NOTICE OF ALLOWANCE, AND SERIAL NUMBER.

Attachments:

- ☒ Examiner's Amendment
- ☒ Examiner Interview Summary Record, PTOL-413
- ☒ Reasons for Allowance
- ☐ Notice of References Cited, PTO-892
- ☐ Information Disclosure Citation, PTO-1449
- ☐ Notice of Informal Application, PTO-152
- ☐ Notice re Patent Drawings, PTO-948
- ☐ Listing of Bonded Draftsmen
- ☐ Other

RAYMOND G. HENLEY III
PRIMARY EXAMINER
GROUP 126 - ART UNIT 125

PTOL-37 (REV. 4-89) *

USCOMM-DC 89-3789

EXAMINER'S AMENDMENT/REASONS FOR ALLOWANCE

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee.

Authorization for this Examiner's Amendment was given in a telephone interview with Philip E. Hansen on July 13, 1994.

The application has been amended as follows:

IN THE CLAIMS:

In claims 1 and 6, line 4, ---chronically--- has been inserted before the word "administering".

In claim 6, line 3, ---chronic administration of racemic--- has been inserted before the word "albuterol"..

IN THE ABSTRACT:

At the last line, ---chronic administration of racemic--- has been inserted before the term "albuterol".

The following is an Examiner's Statement of Reasons for Allowance:

Applicants' amendment and the declaration of T. Scott Johnson filed May 11, 1994 have been received, entered and favorably considered. The Examiner agrees

with the statements made by both applicants and the declarant that support exists in the present specification for avoidance of the side effects associated with chronic therapy for asthma. Moreover, it is the Examiner's opinion that it would not have been expected from the prior art of record that the R(-) isomer of albuterol would possess the improved side effect profile as established in the declaration of Dr. Aberg filed July 23, 1993, i.e., that the R(-) isomer of albuterol does not cause the hypersensitivity reaction normally associated with long-term racemic albuterol administration in patients suffering from asthma. This fact is highly significant and compels the Examiner to conclude that the presently claimed invention would not have been obvious under 35 U.S.C. § 103. The Examiner is guided in his opinion by the finding of the Board of Patent Appeals and Interferences in the unpublished decision of Ex parte Ferrari et al. (Appeal No. 629-61) dated January 28, 1987 in which a similar factual situation existed. Further comments relating to this decision as well as the significance of the hypersensitivity reaction associated with racemic albuterol administration, which are hereby adopted by the Examiner, are presented in the paper entitled "Record of Telephonic Interview" filed by applicants on August 5, 1993.

Thus, for the reasons above, claims 1-6 and 8 are deemed to be allowable.

Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

RAYMOND J. HENLEY III
PATENT EXAMINER
GROUP 120 - ART UNIT 125

EXHIBIT 8

SPC89-05'Pre A
RWW12
7/14/92
RWW/bjn

PATENT APPLICATION
Docket No. SPC89-05

#17/A
JK
7/22/9

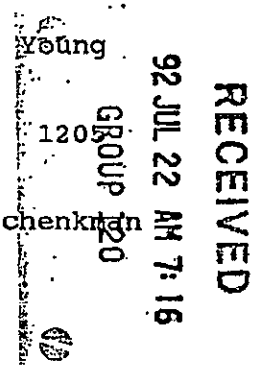
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Timothy J. Barberich and James W. Young

Serial No.: 07/896,725 Group Art Unit: 1205

Filed: June 9, 1992 Examiner: L. Schenkman

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL



CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to Honorable Commissioner of Patents and Trademarks, Washington, D.C. 20231 on 7-14-92

Hamilton, Brook, Smith & Reynolds, P.C.

B.J. Nassi 7-14-92
Signature Date

PRELIMINARY AMENDMENT

The Honorable Commissioner
of Patents and Trademarks
Washington, D. C. 20231

Sir:

Please amend the above-identified Application as follows:

In the Claims:

In Claim 1, line 6, between "bronchodilation" and the "," insert --while simultaneously reducing undesirable side effects---;

In Claim 6, line 6, between "bronchodilation" and "and" insert ---while simultaneously reducing undesirable side effects---;

In Claim 9, line 2, delete "an optically pure" and instead insert ---the---.

REMARKS

The instant Application is a contination of Application Serial No. 07/461,262 ("the parent case").

The above amendments to the Claims have been made to more distinctly claim the subject matter of the invention. Support for these amendments can be found on page 2, line 6-page 3, line 6; page 3, lines 8-14; and page 6, lines 14-27 of the specification. The relationship between these amendments to the Claims and the response to the Office Action of December 9, 1991 in the parent case will be more fully explained below.

Rejection of Claims 1-6, 8, 9, 13 and 14 under 35 U.S.C. §103.

Claims 1-6, 8, 9, 13 and 14 were rejected under 35 U.S.C. §103 over Chemical Abstracts which, as previously stated by the Examiner, teaches salbutamol (albuterol) used to treat asthma and compositions containing albuterol. The case, In re Adamson et al., was cited as teaching that the difference in activity between isomers is not unexpected.

Applicants respectfully submit that the claims, as amended, overcome the rejection. The Chemical Abstracts reference shows the bronchodilation effects of salbutamol and drug combinations incorporating salbutamol. However, this reference does not teach the use of a quantity of the R(-) isomer of albuterol sufficient to cause bronchodilation while simultaneously reducing undesirable side effects associated with racemic albuterol.

Although In re Adamson et al. teaches that optical isomers themselves are unpatentable over compounds that the art recognizes as having optical isomers, it is not correct to assume from this that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides therapeutic effects without causing undesirable side effects.

One would be led to assume, from the Examiner's apparent interpretation of In re Adamson et al., that the physiological effects of a racemic compound, both therapeutic and adverse, are elicited by the same isomer. However, this assumption is contrary to Applicants' disclosure which teaches that undesirable side effects are associated with the racemic mixture or the therapeutically inactive isomer, i.e. the S(+) isomer, of albuterol, but not with the R(-) isomer. Applicants have, therefore, made the unexpected disclosure that the claimed isomer does not have the same type of activity as the racemic mixture.

Rejection of Claims 1-5 under 35 U.S.C. §103.

Claims 1-5 have been rejected under 35 U.S.C. §103 as being unpatentable over Brittain et al., Hartley et al., Hawkins et al., and Buckner et al. who, as previously stated by the Examiner, teach compositions containing the claimed compounds with its isomers used as a bronchodilator in the treatment of asthma and, further, that the R(-) isomer has greater bronchodilation activity over the S(+) isomer.

Applicants respectfully submit that the Claims, as amended, also overcome this rejection. In addition to a complete lack of agreement among the cited references concerning the relative efficacies of the R(-) isomer and the racemate, there is no teaching in these references regarding the administration of a quantity of the R(-) isomer sufficient to effect bronchodilation but without

causing undesirable side effects. The references do not indicate that undesirable side effects can be minimized by administering one of the isomers. Only Applicants' disclosure reveals and claims this important method by administering the R(-) isomer of albuterol.

Rejection of Claims 6, 8, 9, 13 and 14 under 35 U.S.C. §103.

Claims 6, 8, 9, 13 and 14 have been rejected under 35 U.S.C. §103 as being unpatentable over Brittain et al., Hartley et al., Hawkins et al. and Buckner et al. in view of Chemical Abstracts which, as previously stated by the Examiner, shows combinations of drugs, including salbutamol, used in the treatment of asthma.

Applicants respectfully traverse this rejection, particularly as applied to the presently amended Claims. Although drug combinations including racemic salbutamol are shown in Chemical Abstracts, there is no indication that a combination containing the R(-) isomer minimizes the undesirable side effects associated with the racemic mixture of albuterol. The combination of the other cited references also does not show this element. The combination of drugs which includes the R(-) isomer would not be obvious since undesirable side effects would be expected to be associated with it; there would be no benefit associated with using the R(-) isomer compared with using the racemic mixture. However, Applicants' disclosure shows that undesirable side effects are minimized when the R(-) isomers used. Thus, the combination of drugs including R(-) albuterol is not an obvious extension of a combination of drugs including racemic albuterol.

Rejection of Claims 9, 13 and 14 under 35 U.S.C. §112, second paragraph.

Claims 9, 13 and 14 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. It was stated that Claims 13 and 14 do not have proper antecedent support in Claim 9. Claims 9, 13 and 14 were also rejected as being too broad absent recitation of amounts of ingredients present.

Claim 9 has been presently amended to remove the phrase "optically pure". It is believed that Claims 13 and 14 now have proper antecedent basis and specify the amount of purity of the R(-) isomer of albuterol.

Applicants again respectfully traverse the rejection of Claims 9, 13 and 14 because recitations of amounts of ingredients are dependent on a number of physiological factors which make specification of quantities uncertain until the physiological features are known. It is submitted that skilled artisans, when these features are known, can determine the amounts of ingredients based on these physiological factors.

CONCLUSIONS

With the above amendments and for the above stated reasons, Applicants believe the 35 U.S.C. §§103 and 112, second paragraph rejections have been overcome. Applicants respectfully request reconsideration of the Application and allowance thereof.

If the Examiner feels that a telephone conversation would expedite the prosecution of this Application, he is asked to call Applicant's Agent at (617) 861-6240.

Respectfully submitted,

Richard W. Wagner

Richard W. Wagner
Registration No. 34,480
Agent for Applicant

Lexington, MA 02173
Dated: July 14, 1992

EXHIBIT 9

WINSTON & STRAWN LLP

Electronic Letterhead

35 W. WACKER DRIVE, CHICAGO IL 60601-9703
TELEPHONE: 312-558-5600 FACSIMILE: 312-558-5700

200 PARK AVENUE NEW YORK, NY 10166 212-294-6700
1700 K STREET, N.W. WASHINGTON, DC 20006 202-282-5000
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101 CALIFORNIA STREET SAN FRANCISCO, CA 94111 415-591-1000
100 NORTH TRYON STREET CHARLOTTE, NC 28202 704-350-7700
43 RUE DU RHONE 1204 GENEVA, SWITZERLAND 41-22-317-75-75
25 AVENUE MARCEAU 75116 PARIS, FRANCE 33-1-53-64-82-82
99 GRESHAM STREET LONDON, UNITED KINGDOM EC2V 7NG 44-020-7105-0000

VIA E-MAIL

March 26, 2008

Preston K. Ratliff II
Paul, Hastings,
Janofsky & Walker LLP
75 East 55th Street
New York, NY 10022

Re: Sepracor v. Barr

Dear Mr. Ratliff:

I am writing regarding the claim construction briefing in this case. As a preliminary matter, I again reiterate that Sepracor must produce all expert reports (with exhibits), interrogatory responses, and depositions (including video recordings) from the Breath and Dey cases to give Barr the opportunity to catch up with the accelerated schedule. That was the deal. Yet at this point, with two weeks left before *Markman* briefing, Sepracor still has not provided all of these requested materials, contrary to its agreement to produce them, and contrary to its representation to the Court that it would do so.

Surprisingly, I also learned today from the letters your colleague forwarded that the parties in the Dey case exchanged only claim terms to be construed, and not proposed constructions. I do not understand then the basis for your request that Barr should provide more information, when it has not been done in the Dey case pending for over a year longer. Still, per our agreement and in the spirit of cooperation, Barr submits the following proposed claim terms for briefing. Per our agreement, Sepracor is to provide tomorrow its proposal for claim terms, and the parties will then discuss tomorrow to see if any resolution can be reached.

Patent Claim	Claim term	Proposed construction (based on the intrinsic evidence)
'755: 1	side effects associated with chronic administration of racemic albuterol	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac

		arrhythmia) associated with chronic administration of racemic albuterol. See column 3, lines 28-31.
	comprising chronically administering	Comprising prophylactically administering
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'994:1	A method of treating an acute attack of asthma	A method of treating an acute attack of asthma (a short and sharp course, not chronic)
	side effects associated with the acute administration of racemic albuterol,	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with the acute administration (not chronic) of racemic albuterol. See column 3, lines 28-31.
	suffering from an acute attack of asthma	Experiencing an asthma attack, such as an episode of coughing, wheezing or gasping. See Aberg I, at ¶5.
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects,	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'090:1	side effects associated with the administration	If capable of being construed:

	of racemic albuterol	Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with the administration of racemic albuterol. See column 3, lines 28-31.
	a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	undesirable side effects	See above "side effects" term
	said R isomer being substantially free of its S(+) isomer.	Containing 10% by weight or less of the S(+) isomer of albuterol
'002:1	a quantity of optically pure R(-) albuterol sufficient to induce said bronchodilation.	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
'002:10	the concomitant liability of adverse effects associated with racemic albuterol,	If capable of being construed: Central nervous system effects (such as tremor, nervousness, shakiness, dizziness and increased appetite) and cardiac effects (such as cardiac arrhythmia) associated with chronic administration of racemic albuterol. See column 3, lines 28-31.
	a quantity of optically pure R(-) albuterol sufficient to induce said bronchodilation	A quantity containing 90% by weight or more of the R(-) isomer of albuterol sufficient to result in bronchodilation
	reducing said adverse effects.	See above "side effects" term
'993:1	optically pure R(-) albuterol.	Containing 90% by weight or more of the R(-) isomer of albuterol
'993:10	optically pure R(-) albuterol.	Containing 90% by weight or more of the R(-) isomer of albuterol

For all other claim terms, Barr proposes that they are to be given their plain and ordinary meaning, and objects to and disagrees with Sepracor's proposed constructions (which Sepracor represented are reflected in its response to Barr's Interrogatory No. 1).

Regards,

/s/
Imron T. Aly

EXHIBIT 10

Part #38

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: December 7, 1993 Examiner: R. Henley III

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

DECLARATION UNDER 37 C.F.R. §1.132

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, T. Scott Johnson, declare:

1. I reside at 415 Nashwatuc Road, Concord, Massachusetts.

2. I earned a Bachelor of Science degree from the University of Alabama in 1969 and an M.D. degree from the University of Alabama School of Medicine in 1973. I am certified by the American Board of Internal Medicine with a subspecialty in Pulmonary Disease. I have been a Clinical and Research Fellow in Pulmonary Disease at the University of Colorado Medical Center, and, until 1991 I was Assistant Professor of Medicine at Harvard Medical School, where I was an Attending Consultant in Pulmonary Disease.

3. I am the author of 16 original articles, 8 review articles and a textbook on subjects relating to pulmonary disease.

4. I am presently a Managing Partner of Medical Portfolio Management, Inc., in Cambridge, Massachusetts. In this capacity, I have been retained by Sepracor, Inc.

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(assignee of the above-identified application) as a paid consultant on an hourly basis. My compensation from Sepracor is unaffected by any change in status of the above-identified application, and I will not benefit financially from issuance of a patent thereon.

5. I have reviewed and do understand the contents of the above-identified application, which is directed to a method for treating asthma while avoiding the side effects associated with racemic albuterol by using the pure R-enantiomer of albuterol. As a result of my knowledge and experience I make the following observation:

The term "chronic" does not appear in the specification. However, the concept of chronic administration is implicit in the description of modes of administration that is found in the specification. In particular, on page 4 in the paragraph extending from line 4 to line 13, the concepts of the two modes of therapy (acute and chronic) are discussed. In the first mode (acute) the albuterol is administered "after onset of asthma". In the second, albuterol is administered "prophylactically, that is, before the bronchiospasm [sic] begins in an asthma attack, to prevent its occurrence.."

Asthma is defined (Webster's Medical Desk Dictionary, 1986 edition) as "a condition often of allergic origin that is marked by continuous or paroxysmal labored breathing accompanied by wheezing, by a sense of constriction in the chest, and often by attacks of coughing or gasping". To be noted is the distinction between asthma (a condition or disease state) and an asthmatic attack (an acute episode of coughing, wheezing or gasping), which often accompanies the general disease state. Asthmatic attacks can be treated acutely; asthma is treated chronically.

Albuterol is, in the presently claimed invention, intended to be administered to "an individual who has asthma" (line 5 to 6). Since the patient has asthma (i.e suffers from a disease state), and treatment is to be prophylactic, treatment would have to be chronic. If the treatment were not chronic, cessation of administration might or might not lead to an immediate attack, but it would certainly lead to

reestablishment of the disease condition.

Thus, although the term "chronic" is not used, its implication is clear in the description of prophylactic therapy. Indeed, since one is commonly not able to predict the onset of an acute attack, and since current practice in the treatment of asthma favors the treatment of the underlying disease state, many patients are treated chronically. Thus the person of skill in the art would understand that the application was referring to chronic therapy when it speaks of either prophylactic or periodic administration.

That the concept of chronic medication is envisioned is further supported by the disclosure on page 5, line 6 to line 9, regarding oral therapy. An oral regimen of "1 to about 8 mg two to four times daily" would not make sense as acute therapy.

6. I further declare that all statements of the foregoing declaration made of my own knowledge are true and that all statements made upon information and belief are believed true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above identified application or any patent issuing thereon.

Signed by me this 11th day of May, 1994.

T Scott Johnson

T. Scott Johnson

I:\USERS\PSH\7010272.DEC
May 11, 1994

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MAY 12 1994

EXHIBIT 11

#9 JRH 9/18/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich et al.

Serial No.: 08/335,480 Group Art Unit: 1205

Filed: November 7, 1994 Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE (R) ALBUTEROL

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, June 9, 1995.

Philip E. Hansen
Agent for Applicant
Reg. No. 32,700

Date of Signature: June 9, 1995

Assistant Commissioner for Patents
Washington, D.C. 20231

RESPONSE UNDER 37 C.F.R 1.111

Dear Sir:

This is in response to the Official Action of March 9, 1995 (Paper No. 7). The three-month period for response expires June 9, 1995; this response is therefore timely filed.

AMENDMENTS

Please amend the application as follows:

In the specification:

Page 1, line 2 (following the title and preceding the "Description"), please delete "This application is a continuation of application Serial No. 08/163,581, filed 12/7/93." and replace with

A

-- Cross Reference to Related Applications

This application is a continuation of application Serial No. 08/163,581, filed December 7, 1993 and now U.S. Patent 5,362,755, which was a continuation of application Serial No. 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application Serial No. 07/461,262 filed January 5, 1990, now abandoned.--

In the claims:

Cancel claims 5, 7 and 9-12.

Amend claims 1 and 6 as follows:

1. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, said R isomer being substantially free of its S(+) isomer.

6. (once amended) A method of treating an acute attack of asthma [in an individual with albuterol], while reducing side effects associated with the acute administration of racemic albuterol, comprising administering to [the] an individual suffering from an acute attack of asthma a quantity of an optically pure R(-) isomer of albuterol sufficient to result in bronchodilation while simultaneously reducing undesirable side effects, and at least one additional drug selected from the group consisting of bronchodilators, antihistamines and analgesics.

REMARKS

The specification has been amended to clarify that it claims priority of the great grandparent application and to fully characterize the intervening applications. The claims have been amended to clarify the invention sought to be patented in the present application. The claims have been amended so that they parallel the allowed claims in parent application Serial No. 08/163,581 (Now U.S. Patent 5,362,755); the sole difference is that the claims in the parent related to reducing side effects upon chronic administration and the instant claims relate to reducing side effects associated with acute administration. Support for the amendment is found on page 4, line 4 to line 13. The reference to the administration of albuterol to an individual "after onset of asthma to reduce breathing difficulty" (line 7) reflects acute medication, whereas the reference to prophylactic treatment (line 10) relates to chronic therapy.

Claims 1-12 were presented in the application as filed. Claims 5, 7 and 9-12 are canceled by amendment above. Claims 1-4, 6 and 8 are therefore pending in the application.

In the Office Action of March 9, 1995, all of the claims were rejected as obvious over Muittari et al. (CK) in view of Brittain et al. (CB), Hawkins et al. (CD) and Hartley et al. (CC). The rejection is traversed. Applicants' position on what the cited art fairly teaches was presented in their Preliminary Remarks, submitted December 7, 1993, in the parent case and reiterated below.

The Muittari reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the

reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the Examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for β_2 receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle (β_2) vs atrial muscle (β_1) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in β_2 receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is 0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on β_2 receptors rather than β_1 receptors. The effects of the R isomer and the racemic mixture are equiactive on β_2 receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with

regard to selectivity between β_1 and β_2-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative selectivity could be drawn.

Putting all this together: Hawkins et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references, but by discarding all the data that don't conform to the desired conclusion, it is possible to conclude that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. The Examiner reaches this conclusion with respect to the teachings of the references in the Office Action of March 9. For the sake of the arguments below, applicants assume that the R enantiomer is twice as potent as the racemate, although they question whether the cited references establish this.

As long as S-albuterol is totally inert ballast, a two-fold potency enhancement is of no practical consequence: a process for the resolution of racemic albuterol would

inevitably produce R-albuterol in less than 50% yield, whereas the use of the racemic albuterol would, at worst, provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. As stated in European patent application 256586 (page 2, line 8), "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity."

Testa and Trager [Chirality 2, 129-133 (1990)] have created a decision tree to aid in deciding whether to develop a racemic pharmaceutical or a single enantiomer. A copy of the reference is submitted herewith as Exhibit A. If it were the case that it would always be obvious to develop a single enantiomer, there would be no need for Testa and Trager's decision tree. As they make clear, the mere fact that enantiomers exist is not justification for administering a single enantiomer; moreover, even the fact that one of the two enantiomers is more potent is not determinative. They state

> "While it is abundantly clear that a racemic mixture must be considered as the mixture of two pharmacologically distinct entities, it is also clear that this view, in and of itself, does not infer any value judgement. Such judgment awaits the light of scientific fact and it is only in this context that any decision as to develop a racemate or a eutomer as a new drug is convincingly founded."

The scientific facts referred to by Testa and Trager as they relate to albuterol were shown in the cited references to result in the judgment that the racemate was the proper entity to develop, and although both enantiomers have been known in the art for 24 years, neither has ever been developed as a pharmaceutical.

In the Office Action of March 9, 1995, the Examiner cited *In re Adamson*. Although *In re Adamson* suggests that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. [See, for example, U.S. patent 4,851,444 (Exhibit B), issued 29 years after Adamson, whose claims cover a method for using S-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.]

In the present case, applicants claims relate to a new use, namely a method for treating asthma while simultaneously reducing side effects associated with the administration of racemic albuterol. The unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, and is not suggested by any of the references. [That the references singly and in combination suggest that there would be no diminution of side effects is fully argued in the Declaration Under 37 C.F.R. 1.132 of February 8, 1993, by Dr. Gunnar Aberg, submitted with the response of February 10, 1993, in the grandparent case 07/896,725. A copy of that declaration is enclosed herewith as Exhibit C, and attention is drawn to page 5.] References do exist that suggest an advantage to R-albuterol over racemic albuterol for the reduction of side effects [Morley et al. and Chapman et al., of record in the parent case], but they were published more than a year after the priority date of the instant application, and merely add support to the patentability of the claims in the parent '581 application.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art". In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. This is considerably more than is "suggested by the prior art"; on the contrary, the art suggests that there would be no reduction in side effects. In contradistinction to the premise in *Adamson*, where presumably the art is silent, in the present case the art teaches away. Thus, the decision in *Adamson* is not controlling in this situation.

Against this background in the parent case, Examiner Henley concurred with applicants that the use of R-albuterol to treat asthma while avoiding the side effects associated with chronic administration was nonobvious. However, he did not believe that applicants' showings were sufficient to support that portion of the claimed subject matter that related to side effects associated with acute administration of racemic albuterol. For that reason he would only allow claims restricted to chronic administration. Applicants now seek to complete the original breadth of the claims, and in support thereof, submit herewith the Declaration Under 37 C.F.R. 1.132 of Dr. Dean A. Handley.

The declaration of Dr. Handley establishes that by removing the S enantiomer one maintains the bronchodilatory effects exhibited by racemic albuterol for acute therapy of asthma attacks, while simultaneously avoiding or mitigating the major side effect observed in acute therapy. To summarize briefly, Dr. Handley shows that R-albuterol produces potent

and acute bronchodilation in stable asthmatic patients. The onset of action is rapid and persists for 3 hours. R-Albuterol provides acute, symptomatic treatment and relief for conditions of asthma and bronchitis. S-albuterol is essentially without effect.

On the other hand, both individual enantiomers and racemic albuterol induce sustained tremors in animals. The preclinical observations on the relative abilities of the albuterol enantiomers to provoke tremors upon single dose, acute administration were quite unexpected. Skeletal muscle tremor is one of the most common side effects of ordinary doses of all marketed β_2-agonists. The studies reported in the declaration demonstrate that, unlike the R enantiomer, the tremorigenic liability associated with the S enantiomer is not balanced by a corresponding efficacy in producing bronchodilation. This presents a clear rationale for employing the pure R enantiomer, substantially free of the S enantiomer, in acute therapy of asthma attacks. By removing the S enantiomer, one maintains the bronchodilatory effects of racemic albuterol while providing only half the tremorigenic dose.

In light of the foregoing amendments, declaration and explanation, it is believed that the claims are allowable, and reconsideration of the rejection is respectfully requested.

The Office Action of March 9, 1995, also included a rejection of claims 1-8 under the judicially created doctrine of double patenting of the obviousness type. In the parent case, over which the unamended claims were rejected, the Examiner took the position that applicants' declarations were sufficient to establish the unexpected utility of R-albuterol in avoiding side effects associated with chronic therapy, but not those side effects associated with acute therapy.

Implicit in the earlier requirement to limit the claims to chronic therapy was the assumption that the fact that effects were demonstrated in chronic therapy did not suggest that those same advantages would be observed in acute therapy. If advantages in chronic therapy would not predict advantages in acute therapy, applicants believe that by amending the claims to limit them to side effects associated with acute therapy, they have now eliminated the overlapping obvious subject matter, and the double patenting obviousness rejection would no longer apply.

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
Registration No. 32,700

Dated: June 9, 1995

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5 Columbia Circle
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EXHIBIT 12

Stedman's

MEDICAL DICTIONARY

25th Edition

ILLUSTRATED

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Accurate indications, adverse reactions, and dosage schedules for drugs are provided in this book, but it is possible that they may change. The reader is urged to review the package information data of the manufacturers of the medications mentioned.

Printed in the United States of America

English Language Co-editions
Asian 1967, 1972, 1976
Indian 1967, 1973
Taiwan 1972, 1978

Translated Editions
Greek 1976
Indian 1977
Japanese 1977, 1985
Portuguese 1976
Spanish (in press)

Library of Congress Cataloging-in-Publication Data

Stedman, Thomas Lathrop, 1853–1938.
[Medical dictionary]
Stedman's medical dictionary.—25th ed.
p. cm.
ISBN 0-683-07916-6 REGULAR EDITION
ISBN 0-683-7925-5 DELUXE EDITION
1. Medicine—Dictionaries. I. Title. II. Title: Medical dictionary
[DNLM: 1. Dictionaries, Medical. W 13 S812m]
R121.S8 1989
610'.3—dc20
DNLM/DLC
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89-16579
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the inflammation into peribronchiolar alveoli and the alveolar ducts; may become confluent or may be hemorrhagic.

tuberculous b., an acute form of pulmonary tuberculosis characterized by widespread patchy consolidations.

bronchopulmonary (brong-kō-pul'mō-nār-ē). Relating to the bronchi tubes and the lungs.

bronchorrhaphy (brong-kōr'ă-fē) [broncho- + G. *raphē*, a seam]. Suture of a wound of the bronchus.

bronchorrhea (brong'kō-rē'ă) [broncho- + G. *rhoia*, a flow]. Excessive secretion of mucus from the bronchial mucous membrane.

bronchoscope (brong'kō-skōp) [broncho- + G. *skopeō*, to view]. An endoscope for inspecting the interior of the tracheobronchial tree, either for diagnostic purposes (including biopsy) or for the removal of foreign bodies.

bronchoscopy (brong-kos'kŏ-pē). Inspection of the interior of the tracheobronchial tree through a bronchoscope.

bronchospasm (brong'kō-spazm). Contraction of smooth muscle in the walls of the bronchi and bronchioles, causing narrowing of the lumen.

bronchospirochetosis (brong'kō-spī'rō-kē-tō'sis). Hemorrhagic *bronchitis*.

bronchospirography (brong'kō-spī-rog'ră-fē) [broncho- + L. *spiro*, to breathe, + G. *graphō*, to write]. Use of a single lumen endobronchial tube for measurement of ventilatory function of one lung.

bronchospirometer (brong'kō-spī-rom'ĕ-ter) [broncho- + L. *spiro*, to breathe, + G. *metron*, measure]. A device for measurement of rates and volumes of air flow into each lung separately, using a double lumen endobronchial tube.

bronchospirometry (brong'kō-spī-rom'ĕ-trē). Use of a bronchospirometer to measure ventilatory function of each lung separately.

bronchostaxis (brong'kō-stak'sis) [broncho- + G. *staxis*, a dripping]. Hemorrhage from the bronchi.

bronchostenosis (brong-kō-sten-ō'sis). Chronic narrowing of a bronchus.

bronchostomy (brong-kos'tō-mē) [broncho- + G. *stoma*, mouth]. Surgical formation of a new opening into a bronchus.

bronchotome (brong'kō-tōm) [broncho- + G. *tomē*, a cutting]. An instrument for incising a bronchus.

bronchotomy (brong-kot'ō-mē). Incision of a bronchus.

bronchotracheal (brong-kō-trā'kē-ăl). Relating to the trachea and bronchi.

bronchovesicular (brong'kō-vĕ-sik'yū-lăr). Bronchoalveolar; relating to the bronchioles and alveoli in the lungs.

bronchus, pl. bronchi (brong'kŭs, brong'kī) [Mod. L., fr. G. *bronchos*, windpipe] [NA]. One of the subdivisions of the trachea serving to convey air to and from the lungs. The trachea divides into right and left main bronchi which in turn form lobar, segmental, and subsegmental bronchi. In structure, the intrapulmonary bronchi have a lining of pseudostratified ciliated columnar epithelium, and a lamina propria with abundant longitudinal networks of elastic fibers; there are spirally arranged bundles of smooth muscle, abundant mucoserous glands, and in the outer part of the wall irregular plates of hyaline cartilage.

eparterial b., obsolete term for the right superior lobe b. which passes above the right pulmonary artery.

hyparterial bronchi, obsolete term for those bronchi which pass below the pulmonary arteries, *i.e.*, right middle and inferior lobar bronchi and left superior and inferior lobar bronchi.

intermediate b., b. intermedius, the portion of the right main b. between the upper lobe b. and the origin of the middle and inferior lobe bronchi.

left main b., b. principalis sinister.

lobar bronchi, bronchi lobares.

bronchi loba'res [NA], lobar bronchi; the divisions of the bronchi that supply the lobes of the lungs; **b. lobaris superior, b. lobaris medius,** and **b. lobaris inferior** are the three lobar bronchi on the right; **b. lobaris superior** and **b. lobaris inferior** are on the left. The lobar bronchi divide into segmental bronchi.

primary b., the main b. arising at the tracheal bifurcation and extending into the developing lung of the embryo.

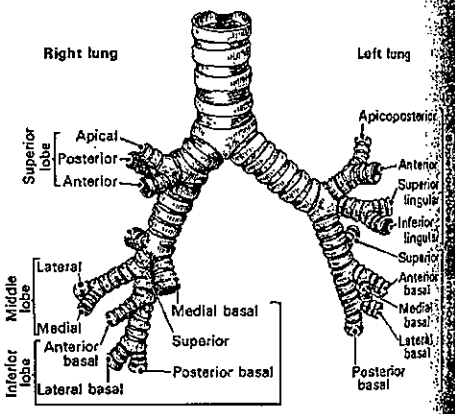
b. principa'lis dex'ter [NA], right main b.; it arises at the bifurcation of the trachea and enters the hilum of the right lung, giving off the superior lobe b. and continuing downward to give off the middle and inferior lobe bronchi.

b. principa'lis sinis'ter [NA], left main b.; it arises at the bifurcation of the trachea, passes in front of the esophagus and enters the hilum of the left lung where it divides into a superior lobe bronchus and inferior lobe b.

right main b., b. principalis dexter.

segmental b., b. segmentalis.

b. segmenta'lis [NA], segmental b.; one of the divisions of a lobar b. that supplies a bronchopulmonary segment. In the right lung there are commonly ten: *in the superior lobe*, b. segmentalis apicalis, b. segmentalis posterior, b. segmentalis anterior; *in the middle lobe*, b. segmentalis lateralis, b. segmentalis medialis; *in the inferior lobe*, b. segmentalis apicalis or superior, b. segmentalis basalis medialis or cardiacus, b. segmentalis basalis anterior, b. segmentalis basalis lateralis, b. segmentalis basalis posterior. In the left lung there are commonly nine: *in the superior lobe*, b. segmentalis apicoposterior, b. segmentalis anterior, b. lingularis superior, b. lingularis inferior; *in the inferior lobe*, b. segmentalis apicalis or superior, b. segmentalis basalis medialis or cardiacus, b. segmentalis basalis anterior, b. segmentalis basalis lateralis, b. segmentalis basalis posterior.



Segmental Bronchi

stem b., the main b. from which the branches of the bronchial tree arise.

Brønsted, Johannes N., Danish physical chemist, 1879–19[illegible]. B. *base, theory.*

brontophobia (bront-ō-fō'bē-ă) [G. *brontē*, thunder, + fear]. Tonitrophobia; morbid fear of thunder.

brood (brūd). **1.** Litter (2). **2.** To ponder anxiously; to meditate morbidly.

Brooke, Bryan N., British surgeon, *1915. See B. *ileostomy*.

Brooke, Henry A.G., British dermatologist, 1854–191[illegible]. See *disease, tumor.*

broom (brūm). Scoparius.

brow [A.S. *brū*]. **1.** The eyebrow. See supercilium. **2.** Fron[illegible]

EXHIBIT 13

REDACTED

EXHIBIT 14

#3A
LB
6/12/98

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich *et al.* Atty Dkt. No.: 0701.027F

Serial No.: Unknown
Continuation of 08/691,604
Filed: August 15, 1996
Group Art Unit: 1205
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR INDUCING BRONCHODILATION USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of ~~our prior copending~~ application 08/691,604, filed August 15, 1996, which ~~was~~ is a now U.S. Patent 5,760,090,

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April 2, 1998

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continuation of application 08/335,480, filed November 7, 1994, now US patent 5,547,994, which ~~was~~ is a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which ~~was~~ is a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

~~13~~. (New) A method of inducing bronchodilation or providing relief of bronchospasm, comprising administering to an individual a quantity of optically pure R-(-) albuterol sufficient to induce said bronchodilation.

~~14~~. (New) A method according to Claim ~~13~~, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim ~~13~~, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

18. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered orally.

19. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

20. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered as a syrup.

21. (New) A method according to Claim 19, wherein the optically pure R(-) albuterol is administered as a syrup.

22. (New) A method of inducing bronchodilation or providing relief of bronchospasm while reducing the concomitant liability of adverse effects associated with racemic albuterol, comprising administering to an individual a quantity of optically

pure R-(-) albuterol sufficient to induce said bronchodilation while simultaneously reducing said adverse effects.

REMARKS

The present application is a continuation of US application, serial number 08/691,604. Claims 1-12 were present in the application as filed. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-22 are therefore pending in this continuation application.

In the parent application, 08/691,604, claims were allowed to "a method of treating asthma". New claims 13-22 relate to "a method for inducing bronchodilation or providing relief of bronchospasms". Support for the new wording relating to inducing bronchodilation or providing relief of bronchospasms is found on page 5, line 5-6, page 3, line 8-9 and elsewhere in the specification. Applicants respectfully submit that new claims 13-22 are allowable with a terminal disclaimer for reasons of record in parent application 08/691,604.

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In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

Philip E. Hansen
Agent for Applicants
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Dated: April 21, 1998

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April 2, 1998

EXHIBIT 15

Lung (1990) Suppl:154–167

Lung

Long-term Management of Reversible Obstructive Airways Disease in Adults

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Abstract. The goals of the long-term management of reversible obstructive airways disease (ROAD) are to find the minimum treatment that controls symptoms, allows resumption of normal life, prevents severe attack and death, and controls airflow obstruction. ROADs include asthma, chronic bronchitis, and emphysema. Although the differential diagnosis between these different entities may be difficult, they share the same possibilities of pharmacotherapy, including bronchodilator and antiinflammatory drugs. β_2-agonists administered via inhaled route produce the best bronchodilator/side effects ratio, provided that the drugs reach the bronchi. This underlines the importance of a proper inhalation technique when using a metered-dose inhaler. In patients with hand-breath coordination problems, powder inhalers or spacer devices are useful to ameliorate the therapeutic efficacy of inhaled drugs. Anticholinergic agents are usually less potent bronchodilators than inhaled β_2 agonists in asthma, but they may have additive effects when associated with β_2 agonists. Only a therapeutic trial with peak-flow monitoring can demonstrate the efficacy of anticholinergic drugs in individuals. Theophylline's kinetics are characterized by a narrow therapeutic index with high inter- and intraindividual variabilities. Sodium cromoglycate and nedocromil sodium are antiallergic drugs, the efficacy of which has been demonstrated in controlled studies. Corticosteroids are the most efficient anti-asthma drugs. Inhaled corticosteroid dosing should be tailored to each individual. If inhaled corticosteroid therapy is used in an oral corticosparing attempt, patients should be followed-up during several months. The management of ROAD includes the diagnostic procedures, the identification of triggers and inducers of airways obstruction, the assessment of severity of the disease, and then the treatment and education of the patient. Strategy design to achieve proper use of drugs by patients is discussed.

Offprint requests to: Dr. A. Lurie, Institut de Recherche Thérapeutique (IRT-Eclimed), Hôpital Universitaire Cochin, 27 rue du faubourg St. Jacques, 75674 Paris Cedex, France.

Key words: Bronchial obstruction—Asthma—Reversible obstructive airways disease—Aerosols—Treatment.

Introduction

Reversible obstructive airways disease (ROAD) include asthma, chronic bronchitis, and emphysema. The diagnosis of asthma rests upon anamnestic arguments. If the clinical features are not typical of asthma, the diagnosis may be helped by looking for diurnal variation of peak expiratory flow values or, according to the results of baseline pulmonary test functions, by measuring response to either nonspecific stimuli such as histamine and methacholine, or to an inhaled β_2-agonist. Clear-cut differentiation between chronic bronchitis, emphysema, and asthma is sometimes impossible. Some patients with chronic bronchitis or emphysema present important bronchial reversibility [1]. In contrast, some patients with asthma present little bronchial reversibility in acute trials and their bronchial obstruction may tend to diminish with time [2]. Comparing the pulmonary function tests before and after an acute bronchodilator administration is of limited value if one wants to separate chronic obstructive lung disease from asthma. Furthermore, some patients who appear at first to be relatively unresponsive to β_2-agonists may respond later to repeated bronchodilator challenges [3]. A trial with corticosteroids may be required to insure that reversibility has not been underdiagnosed [4]. If the trial does not show any improvement of bronchial obstruction, corticosteroids may be stopped within 3 days [4]. In contrast, when bronchodilation is observed, inhaled corticosteroids are indicated. If a trial with inhaled corticosteroids is decided, high dosages should be used, because they have been shown to produce better therapeutic effects [5]. The patients with bronchial response to corticosteroids are then mostly managed in a similar way to patients with asthma [6].

One must write or talk with modesty about the management of asthma because although the modern pharmacotherapy of the disease may be highly efficient, more patients die of bronchial asthma than previously. The increasing mortality in patients with asthma during the last three decades did not receive clear explanations [7, 8]. Each hypothesis aiming to elucidate this increased mortality may appear unlikely or insufficient to explain all the available data. These hypothesis belong either to the epidemiology (change in classification of asthma in 1979, increased prevalence and more virulence of asthma, shift in the age distribution of incidence), or to the management of the disease (inadequate assessment and treatment, iatrogenicity) [8].

Pathophysiologic Features of ROADs and Their Therapeutic Implications

Bronchial inflammation and bronchial smooth muscle spasm are the two main pathophysiologic components of asthma [9]. Release of spasmogenic and/or inflammatory mediators from cells in the airways produces and maintains the bronchial pathologic alterations observed in asthma. These cellular mecha-

nisms are better understood in allergic asthma, where the mediators released after the allergenic contact have been shown to recruit inflammatory cells. In turn, these cells release other mediators with inflammatory and spasmogenic actions [9]. Bronchial inflammation has been shown to play an important role in the mechanisms underlying bronchial hyperreactivity, bronchial obstruction, and the symptoms of asthma. ROADs other than asthma may also implicate bronchial smooth muscle spasm and bronchial inflammation associated with irreversible forms of airway obstruction such as loss of bronchial elastic recoil and fibrotic distortion. The pharmacotherapy of ROAD results from these pathophysiologic features. Treatments include bronchodilator and anti-inflammatory drugs.

Pharmacotherapy of ROAD

Bronchodilator Drugs

The therapeutic efficacy of bronchodilators depends upon their dose. Increasing the dose of a bronchodilator may increase also its adverse effects. These adverse effects have been incriminated in the increase in mortality of asthma [8].

β_2 agonists. β_2 agonists are available for inhaled, oral, and parenteral administration. The oral route produces a more delayed onset of action than inhaled or parental route [10]. Oral and parenteral routes produce more pronounced side effects than the inhalation route [11]. Furthermore, the inhaled dose is much lower than that required when the drug is prescribed per os [12]. Therefore, inhalation of β-adrenergic agents produces the greatest benefits/side-effects ratio and is to be preferred for the treatment of ROAD. The importance of a good inhalation technique is discussed further on. Uncontrolled self-treatment with inhaled β_2-agonists may lead to excessive and unsupervised abuse that may delay hospital admission and anti-inflammatory treatment or that may even induce fatal cardiotoxicity [13]. Increase in deaths from asthma in New Zealand has been hypothesized to be due to overuse of high dose of β_2-agonists with home nebulizers and a subsequent underuse of an appropriate anti-inflammatory treatment [14].

The presently available inhaled β_2-agonists produce rapid bronchodilation, which reaches its maximum effect at about 15 min after inhalation and lasts for up to 6 h. They are prescribed at a dose of one to two puffs every 4–6 h. Two puffs should be taken 1 min apart. Patients should be instructed not to exceed 10–12 puffs daily. If a higher daily dose is required, therapeutic adjustment is preferable than to merely increase the daily number of puffs of β_2-agonists. The use of β-adrenergic agonists should not delay the use of corticosteroids, even if rapid relief from symptoms is obtained that diminishes the awareness of the patients about their disease [13].

Slow-release theophyllines. The bronchodilator effect of theophylline is directly related to the serum concentration of the drug. The optimal and safe effects of theophylline are observed at serum concentrations ranging from 7 to 15 μg/ml. Theophylline toxicity is well documented above the "safe" levels of serum concentrations of the drug. Side effects occur frequently following a loading dose and are avoidable when the treatment is started with low doses [15]. However, side effects may appear even within the subtherapeutic serum theophylline concentration range. The combination of slow-release theophylline with β-adrenergic agonists may produce additive therapeutic effects but is susceptible to more pronounced side effects [16]. Difficulties in the management of theophylline treatment are increased by factors that influence theophylline pharmacokinetics such as smoking, age, food, and drugs. The great intra- and intersubject variability in theophylline pharmacokinetics shows the importance of checking serum theophylline concentration in each individual.

Anticholinergic agents. Ipratropium bromide (Atrovent) and oxytropium bromide (Tersigat, Oxivent) are synthetic quaternary ammonium, chemically close to atropine. At present, no major side effects other than bitter taste have been reported for inhaled ipratropium, even if administered at very high doses. In stable asthma, the degree of bronchodilatation obtained with anticholinergic drugs is less than that obtained with β_2-agonists [17]. However, some patients with ROAD respond better to anticholinergic drugs than to β_2-agonists [18]. Factors that favor the good response to ipratropium bromide are nonallergic asthma, old age with long duration of asthma history, and mild bronchial obstruction [19]. The only way to identify a good responder is to perform a trial with the anticholinergic drug [20]. The optimal bronchodilatation following administration of ipratropium bromide is achieved after inhalation of 80 μg [17]. However, doses of 160 μg of ipratropium have been reported to reduce significantly the morning fall in peak expiratory flow rate of patients with asthma [21]. Following an inhaled dose of ipratropium, maximal bronchodilatation is observed in about 1–2 h. In chronic asthma, ipratropium bromide is prescribed at doses of two to three puffs every 4–6 h. Combined treatment with ipratropium bromide and β_2-agonists or theophylline has generally an enhanced or more prolonged effect than each treatment alone [22]. A pressurized aerosol containing both fenoterol and ipratropium bromide is currently available.

Nonbronchodilator Drugs

Nedocromil sodium and sodium cromoglycate. Sodium cromoglycate and nedocromil sodium share the same antiallergic properties [23]. They both inhibit the immediate bronchoconstriction induced by stimuli such as exercise, or inhalation of antigen, sulfur dioxide, or cold air [24, 25]. These agents can also attenuate the late asthmatic reactions in patients with allergic asthma [24]. In adult patients with chronic asthma, treatment with inhaled sodium cromoglycate resulted in significant improvement in asthmatic symptoms and peak ex-

piratory flow rates, as well as reduction in concomitant medications when compared to a placebo group [26]. Nedocromil sodium was shown to improve significantly asthmatic symptoms and lung functions in a placebo-controlled trial of 12 weeks in patients maintained on bronchodilators [27]. Nedocromil sodium has been shown to be effective in the treatment of ROAD, but its place in the strategy of treatment of asthma remains to be determined. Presently, sodium cromoglycate is considered as a first-line prophylactic treatment of asthma.

Corticosteroids. Corticosteroids constitute the most efficient anti-inflammatory drugs. Inhaled corticosteroids produce far less side effects than oral corticosteroids [28]. Inhaled doses up to 1000 μg/day of beclomethasone dipropionate may be used with minimal risks of side effects such as oral candidiasis and dysphonia. These local side effects may be minimized by rinsing the mouth and throat after each inhalation and by using a spacer device [29]. Systemic side effects of inhaled corticosteroids are infrequent up to a daily dose of 1500–2000 μg/day. At doses up to 1500 μg/day, 91% of patients treated with inhaled corticosteroids were shown to have both normal values of morning cortisol and normal response to adrenocorticotropic hormone [30]. Controlled clinical trials in asthmatic patients have demonstrated the therapeutic efficacy of all the presently available inhaled corticosteroids, namely, beclomethasone dipropionate, flunisolide, budesonide, and triamcinolone [31]. A relationship between dose and efficacy of inhaled corticosteroids has been reported. Treatment with inhaled corticosteroids may allow to decrease oral corticosteroids. The success rate of patients weaned off oral prednisone after a long-term administration of inhaled corticosteroids has been estimated by Toogood et al. using data from published studies [32]; the success rate has been found to reach 100% in studies of 4 months or less, while the averaged rate over a period of 24 months of follow-up was about 30%. Oral corticosteroids should be withdrawn with caution because fatal relapse of asthma may occur [33]; this indicates the importance to follow-up the weaning period with peak expiratory flow monitoring. The dosing regimen of inhaled corticosteroids has been a matter of controversy, probably due to differences in the groups studied: 2–4 times per day have been proposed [34]. Patients who present severe exacerbations of asthma during treatment with inhaled corticosteroids require oral or parenteral corticosteroids.

Other agents. So far, calcium channel blockers and α-adrenoceptor blockers have no defined role in the management of ROAD. The results of administration of prostaglandin E_1 or of several inflammatory mediators antagonists have not demonstrated any clinical efficacy [35]. Immunosuppressive agents such as methotrexate and azathioprine have currently no place in the management of ROAD. Antihistamines may be indicated for diseases associated with asthma such as allergic rhinitis. The data available for potassium channel activators may to consider these agents as potentially useful in the bronchodilator treatment [36]. Inhaled furosemide was shown to reduce allergen-induced asthma

but its place in the treatment of asthma requires further study [37]. In this paper, we will concentrate upon the three classes of bronchodilator drugs and the corticosteroid use in the care of patients with ROAD.

Management of ROAD

The management of ROAD associates the diagnostic procedures, already discussed in this paper, the identification of triggers and inducers of bronchial obstruction and the assessment of severity of the disease which is used to define a strategy of treatment and finally the education of the patient [38].

The Assessment of ROAD

Identification of inducers and triggers. The assessment of patients with ROAD include the investigation of all the pathologic conditions that may influence the course of the bronchial disease and that may be accessible to treatment. Agents that provoke acute exacerbation of asthma are usually referred as "triggers" while those that increase airway responsiveness to other stimuli are called "inducers" of asthma [39]. The first step of anti-inflammatory treatment to be considered is the treatment of triggers and inducers of asthma.

The role of allergy to environmental allergens in patients with asthma remains controversial [40, 41]. However, the prevalence of asthma has been shown to be lower in higher altitude, where the prevalence of positive skin tests to house dust mites is also lower than at the sea level [42]. Increased nonspecific bronchial hyperreactivity or allergen-specific bronchial reactivity has been demonstrated during pollen season in sensitive patients with asthma [43, 44]. Allergic symptoms and numbers of positive-prick skin tests were reported to increase with increasing severity of asthma in children [45]. Besides bronchial allergy, allergic rhinitis and sinusitis are often encountered. The cause-effect relationship between upper airways inflammation and induction of asthma is difficult to establish. Some investigators consider that both sinusitis and asthma are manifestations of the same underlying disease [46]. Others suggest that sinusitis can trigger and may aggravate ROAD [45, 47, 48]. Although few data exist that prove that sinusitis may cause or worsen asthma, it is a usual rule to look for and to treat an associated sinusitis in case of difficult-to-control ROAD.

Respiratory infections often aggravate asthma [49]. Viral infections are very frequent precipitating factors in children and adults with asthma [50]. In a retrospective study over a 1-year period, 19% of adult asthmatic patients admitted to a hospital were shown to have a concomitant respiratory infection [51].

Exercise is one of the most common inducers of asthma crisis. Exercise-induced asthma may be identified in the laboratory by exercise or isocapnic hyperventilation challenge [52]. Single preexercise treatment with inhaled β_2-agonists and/or sodium cromoglycate may prevent exercise-induced asthma [52].

The relationship between asthma and gastroesophageal reflux is well established but poorly understood [53]. Overnight intraesophageal pH study may confirm a suspected reflux [54]. Medical or surgical treatment of reflux can improve asthma [55, 56]. Theophyllines have been incriminated to worsen reflux by dilatating the lower esophageal sphincter, but a recent study reported no aggravation of nocturnal asthma in asthmatic patients with reflux treated by aminophylline [57]. Nonsteroidal anti-inflammatory drugs are the most common cause of drug-induced asthma [58]. The worldwide increasing automedication with nonsteroidal anti-inflammatory drugs may represent a potential danger for asthmatic patients that has not yet been evaluated by appropriate studies [8]. β-adrenergic blockers and antibiotics inducing hypersensitivity are also reported as precipitants of acute asthma attacks [59].

Food hypersensitivity is a less common triggering factor of asthma in adults than in children [59]. In contrast, alcoholic drinks are a frequent trigger of asthma [60]. Many patients with suspected food hypersensitivity have gastrointestinal and respiratory symptoms, but the diagnosis is often difficult to confirm, because there is a lack of highly reproducible tests [61]. Food challenges are difficult to interprete and may provoke anaphylactic reactions [62]. Food-induced asthma may be due to food itself, to the coloring, or to the added preservatives.

Stress, emotional conflicts, and other psychological factors must be considered as aggravating factors in some asthmatic patients [63].

The Treatment of ROAD

Assessing and staging the severity of the disease. The staging of ROAD should be based upon the severity of symptoms, the pattern and the importance of bronchial obstruction, and the amount of bronchodilators required to control the disease. Assessing the severity through the symptoms of the patients may be misleading, because perception of bronchial obstruction varies from patient to patient [64]. Therefore, the physician must look mainly for informations deriving from regular peak expiratory flow monitoring. Bronchial obstruction is a criterion of severity not only by its importance but also by its pattern. Daily measurement of peak expiratory flow rate may allow the classification of the pattern of bronchial obstruction: patients with stable asthma have a stable peak flow close to normal values; brittle asthma is characterized by highly variable peak flow values; deteriorating asthma is characterized by slowly diminishing peak flow values; patients with morning dips have low peak flow values only during the nighttime or the early morning [65]. The high variability of bronchial obstruction is a risk factor for exacerbation of the disease [66]. Current schemas of asthma staging have not been evaluated with appropriate clinical studies and are therefore, difficult to assess in terms of their applicability and their prognostic value. Asthma may be classified as mild, moderate, or severe. Patients with mild asthma have occasionally wheezing or tightness of the chest.

Their peak flow rate is mostly normal. They use occasionally inhaled bronchodilators, in periods with symptoms. Patients with mild asthma should be assessed regularly to confirm the mildness of their disease, because the frontier between mild and moderate asthma is far to be clear [67]. Patients with moderate asthma have daily symptoms and they use bronchodilators on daily basis. Their peak flow is under the limit of predicted value. Patients with severe asthma have prominent wheezing. They have disturbed sleep and morning chest tightness and they have often already been admitted to an hospital for severe exacerbation of their asthma [66]. They need administration more than 4 times a day of inhaled bronchodilators to control their symptoms. Their peak flow is less than 80% of predicted value.

Strategy of treatment. The objectives of treatment are to control symptoms, to allow the patient to pursue a normal life, and to control bronchial obstruction. To achieve these objectives, identified causative factors should be avoided. Although this is not always possible, allergen avoidance must be advised in patients where a specific allergen is identified. Immunotherapy may be discussed, though it has a restricted place in the treatment of asthma. Patients with mild asthma may be treated with inhaled β_2-agonist on demand. In patients with apparently mild asthma but also signs of bronchial inflammation, such as exacerbation of symptoms and bronchial obstruction, one should consider a prophylactic treatment with sodium cromoglycate or low doses of inhaled steroids. When permanent treatment is necessary, patients should not be treated only with bronchodilator drugs but also with anti-inflammatory and bronchodilator agents together. The stepwise plan must take into account the efficacy/side effects ratio of the drugs and the severity of the disease. Anti-inflammatory therapy for patients with mild asthma may begin with a trial of nedocromil or sodium cromoglycate for 3 months. If this trial fails, low doses of inhaled corticosteroids are indicated. The first-line bronchodilator treatment is an inhaled β_2-agonist. The narrow therapeutic index and the need of repeated measurements of theophylline blood level together, place theophylline in the second line of bronchodilator treatment [68]. Patients whose asthma cannot be controlled with the combination of an inhaled β_2-agonist and low doses of inhaled corticosteroids may benefit from the addition of a sustained-release theophylline preparation or anticholinergic drugs, in a therapeutic trial with a peak expiratory flow rate monitoring. Patients whose asthma cannot be adequately controlled with the previous association may benefit from increasing the inhaled dose of corticosteroids up to 2000 μg/day and, if needed, by a short course of oral corticosteroids until control is achieved. When symptoms and bronchial obstruction have been minimized, the treatment should be reduced to the minimum dose allowing to maintain the control of the disease. The optimal treatment is the treatment having the highest efficacy associated with the best tolerance. Regular follow-up and monitoring of peak flow rate are necessary to evaluate the efficacy and tolerance of the therapy and the education of the patients.

The nocturnal increase of asthmatic symptoms has been well documented in many asthmatic patients [69]. Poor pharmacologic control of airways during the nocturnal sleep may partly explain the high incidence of nocturnal asthma fatalities [67]. In these patients, the size of the morning dip may benefit from inhaled corticosteroids or inhaled β_2-agonists justifying a trial with these drugs [70]. However, this is not always the case and further treatment should be assessed, such as slow-release theophylline given once daily before bedtime [71].

Education of Patients with ROAD

Objectives of education. Many studies have emphasized the importance of patient participation in the management of ROAD [72]. Better education has been advocated to prevent severe asthma and death from asthma. The main goals of patient education are to obtain a degree of self-assessment and self-management by the patient. To obtain self-assessment, patients should be aware of the triggering factors of asthma and should be encouraged to avoid them. Self-assessment of the severity of the disease based upon symptoms often leads to underestimation and undertreatment [73]. The use of peak flow-meter permits to overcome of the problem of variable and often inaccurate subjective perception of airway obstruction in asthmatics [74] and enables the physician to assess the efficacy of the treatment. The patient's technique for using peak flow-meter should be checked repeatedly. The measurement of peak expiratory flow rate on daily basis is practical in order to assess bronchial obstruction, but it does not eliminate the need of regular spirometric measurements in the laboratory. Regular follow-up visits may help to supervise patients' self-management and allow the physician to assess the efficacy of the treatment. Teaching of self-management should enable patients to act appropriately in the event of an asthma crisis. They should learn which medication to use, how to practice subcutaneous injection of β_2-agonist, and when to call for medical aid. Educating programs aiming only to improve patients' knowledge of asthma were shown to be inefficient in reducing asthma morbidity in general practice [75]. Interpersonal reinforcement was shown to be more effective in reducing emergency department visits than written appeals in adult asthmatics [76]. A self-management plan based on routine assessment of peak flow was shown to substantially improve both subjective and objective assessment of asthma severity, to diminish symptoms, and to increase baseline lung function [77].

Technique of using inhalers and delivery systems. The rise in the mortality and the morbidity of asthma may be partly due to the undertreatment of the patients [78]. This includes both underestimation of severity by physicians and lack of optimal inhaled therapy. Effective inhalation can be obtained by teaching patients how to use the metered-dose inhaler. Education of patients with asthma takes time and should be regularly checked, because metered-dose inhalers are often misused [79].

The use of metered-dose inhalers needs a "hand-breath coordination" which is often difficult to obtain in certain patients such as children and elderly. The generally accepted proper maneuvers are: (1) shake inhaler, (2) place it 2 cm in front of the open lips, (3) exhale, (4) activate once, (5) inhale slowly and deeply, (6) hold breath for 10 s and breathe out slowly. The next puff is inhaled after a pause of about 1 min [80]. This pause has been shown to improve the bronchodilator efficacy of metered-dose inhalers [81]. The high speed of the inhaled cloud favors proximal deposition, bitter taste, and local side effects [82]. Additionally, numerous technique errors have been recorded [82]. These errors influence therapeutic efficiency, indicating the importance of supervising the inhalation technique both at the time of prescription and afterward [79].

Many patients find it difficult to use a metered-dose inhaler [83]. Hand-breath coordination problems can be overcome by using a spacer devices with the metered-dose inhaler or by the use of dry powder inhalers. The use of a spacer device is simple: The patient actuates the metered-dose inhaler that is attached to the chamber, then inhales the drug from the chamber. One single actuation of the metered-dose inhaler is recommended, to avoid the increased deposition of aerosol in the apparatus, resulting from successive actuations [84]. In patients with obstructive airways disease, the use of spacer devices has been shown to decrease the aerosol deposition in the oropharynx and to increase the deposition in the bronchi [84]. The bronchial response to a β_2 agonist is greater when using a metered-dose inhaler with a spacer device than when using a metered-dose inhaler alone [85]. A spacer device is as effective as a nebulizer in chronic stable asthma [84]. A high dose of inhaled corticosteroid treatment when administered via a spacer is associated with a reduced risk of oropharyngeal candidiasis and with an increased bronchial effect [29]. Patients with asthma requiring the use of spacer devices are those who are not able to use properly inhalers, who need more than 1500 μg beclomethasone per day or equivalent to control their disease, and patients in whom dose-limiting oropharyngeal side effects compromise the usefulness of inhaled corticosteroid therapy [29].

Hand-breath coordination problems may also be overcome by using powder inhalers. Powder inhalers have been shown to be as effective as metered-dose inhalers [87]. However, about 3% of patients with asthma have difficulties in using the powder inhaler properly [88]. The need to replace the capsule before each dosing diminishes the compliance of patients. Inhaler devices equipped with more than one dose of the drug are now available for both salbutamol and beclomethasone. The potential drawbacks of powder inhalers are coughing and proximal deposition. In conclusion, none of the current devices satisfies the needs of all patients and the method of delivery should be chosen for each individual patient.

Conclusion

The optimal long-term management of ROAD is based upon assessment of the diagnosis and the individual risk factors for exacerbation of the disease. The

treatment should be tailored to each individual patient by taking into account the efficacy/safety ratio of the medications. Education of the patient plays a major role in the successful long-term outcome of the treatment. This education should start with self-assessment by the patient, which consists of learning the potential risk factors and learning how to use properly and on a daily basis the peak flow-meter. Then patients should learn how to treat themselves following a stepwise management plan and should know when to call for medical aid.

Presently, most of therapeutic strategies are based upon clinical trials in which patients belong to an homogeneous population that is not representative of the whole population of asthmatic patients. Most published studies are designed to compare the potency of drugs to a placebo or to another drug. Any future improvement in the management of ROAD will be based upon trials that aim to reach a decision and to define a therapeutic strategy [89].

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EXHIBIT 16

#21
2/9/00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Barberich *et al.* Atty Dkt. No.: 0701.027H

Serial No.: Unknown
Continuation of 09/200,541
which was filed: November 25, 1998
Group Art Unit: 1614
Examiner: Henley III, R.

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL

To: Assistant Commissioner for Patents
Box PATENT APPLICATION
Washington, D.C. 20231

Preliminary Amendment Under 37 C.F.R. 1.115

Dear Sir:

Prior to examination, please amend the application as follows:

In the Title:

Please delete "METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-)ALBUTEROL" and substitute therefor --METHOD FOR TREATING BRONCHOSPASM USING OPTICALLY PURE R(-)ALBUTEROL--.

In the specification:

Page 1, between line 2 and line 3, insert:

--Cross Reference to Related Applications

This application is a continuation of our prior copending application 09/200,541, filed November 25, 1998, which is a continuation of application 09/063,551, filed April 21, 1998, now US Patent 5,844,002, which was a continuation of application 08/691,604, filed August 15, 1996, now US Patent 5,760,090, which was a continuation of application 08/335,480, now US patent filed November 7, 1994,

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December 8, 1999

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5,547,994, which was a continuation of application 08/163,581, filed December 7, 1993, now US patent 5,362,755, which was a continuation of application 07/896,725, filed June 9, 1992, now abandoned, which was a continuation of application 07/461,262, filed January 5, 1990, now abandoned.--

In the Claims:

Cancel claims 1-12.

Please add the following claims:

13. (New) A method of treating bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

14. (New) A method according to Claim 13, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

15. (New) A method according to Claim 13, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

16. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered by inhalation.

17. (New) A method according to Claim 16, wherein the optically pure R(-) albuterol is administered in an amount of

about 30 μg to about 90 μg.

18. (New) A method according to Claim 13, wherein the optically pure R(-) albuterol is administered orally.

19. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

20. (New) A method according to Claim 18, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

21. (New) A method according to Claim 19, wherein the optically pure R(-) albuterol is administered as a syrup.

22. (New) A method of preventing bronchospasm in a patient with reversible obstructive airway disease, comprising administering to said patient a therapeutically effective amount of optically pure R-(-) albuterol.

23. (New) A method according to Claim 22, wherein the albuterol comprises at least 90% by weight of the R(-) isomer and not more than 10% by weight of the S(+) isomer.

24. (New) A method according to Claim 22, wherein the albuterol comprises at least 99% by weight of the R(-) isomer and 1% or less by weight of the S(+) isomer.

25. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered by inhalation.

26. (New) A method according to Claim 25, wherein the optically pure R(-) albuterol is administered in an amount of about 30 μg to about 90 μg.

27. (New) A method according to Claim 22, wherein the optically pure R(-) albuterol is administered orally.

28. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered in an amount of about 1 mg to about 8 mg.

29. (New) A method according to Claim 27, wherein the optically pure R(-) albuterol is administered as a tablet, capsule or syrup.

REMARKS

The present application is a continuation of US application, serial number 09/200,541. Claims 1-12 were present in the original application 07/461,262, from which this application claims ultimate priority. All claims pending in the original application are canceled by amendment above and are replaced by new claims. Claims 13-29 are therefore pending in this continuation application.

In previous applications in this series, claims have been allowed to "a method of treating asthma" (08/691,604), to "a method for inducing bronchodilation or providing relief of bronchospasms" (09/063,551) and to "a method of treating an acute attack of asthma" (08/335,480). Applicants respectfully submit that new claims 13-29 to "a method of treating bronchospasm in a patient with reversible obstructive airway disease" and to a method of preventing bronchospasm in a patient with reversible obstructive airway disease" are allowable with a terminal disclaimer for reasons of record in parent applications 09/063,551 and 08/691,604.

In order to expedite prosecution, Applicants enclose herewith terminal disclaimers in accordance with 37 CFR 1.321 (b) and (c) and fees under 37 C.F.R. 1.20(d).

Respectfully submitted,

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Dated: December 17, 1999

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December 8, 1999